

2. (Twice Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:
- (a) encodes the amino acid sequence shown in SEQ ID NO: 4; and
 - (b) hybridizes to the nucleotide sequence of SEQ ID NO:3 or the complement thereof under highly stringent conditions of 0.5 M NaHPO₄, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1% SDS at 68°C.

Please add new claims 5-10 as follows:

--5. (New) The isolated nucleic acid molecule of claim 1, wherein said isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:3.

6. (New) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.

7. (New) A recombinant expression vector comprising the isolated nucleic acid molecule of claim 1.

8. (New) The recombinant expression vector of claim 7, wherein said isolated nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:4.

9. (New) The recombinant expression vector of claim 8, wherein said isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:3.

10. (New) A host cell comprising the recombinant expression vector of claim 7.--

RESPONSE

I. Status of the Claims

No claims have been cancelled. Claims 1 and 2 have been amended. Claims 5-10 have been added.

Claims 1-2 and 5-10 are therefore presently pending in the case. For the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. In compliance with 37 C.F.R. § 1.121(c)(1)(ii), a marked up copy of the original claims is attached hereto as **Exhibit B**.

II. Support for the Claims

Claim 1 has been amended to recite that the isolated nucleic acid molecule comprises at least 60 contiguous nucleotides from SEQ ID NO:3. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 1 as originally filed and in the specification at page 6, line 8.

Claim 2 has been amended to recite specific highly stringent hybridization conditions. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 2 as originally filed and in the specification on page 4, lines 1-9.

Claim 5 has been added to specifically recite an isolated nucleic acid molecule that comprises the nucleotide sequence of SEQ ID NO:3. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 1 as originally filed.

Claim 6 has been added to specifically recite an isolated nucleic acid molecule that encodes the amino acid sequence of SEQ ID NO:4. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least in claim 2 as originally filed.

Claims 7-9 have been added to specifically recite recombinant expression vectors comprising isolated nucleic acid molecules of the invention. Support for these claims can be found throughout the specification as originally filed, with particular support being found at least at page 13, lines 1-10.

Claim 10 has been added to specifically recite a recombinant expression vector comprising an isolated nucleic acid molecule of the invention. Support for this claim can be found throughout the specification as originally filed, with particular support being found at least at page 13, lines 10-16.

It will be understood that no new matter is included within the amended or newly added claims.

III. Rejection of Claims 1 and 2 Under 35 U.S.C. § 101

The Action first rejects claims 1 and 2 under 35 U.S.C. § 101, as allegedly lacking a patentable utility. Applicants respectfully traverse.

The present invention has a number of substantial and credible utilities, not the least of which is in forensic analysis, as described in the specification, at least at page 10, lines 13-24. As described in the specification at page 15, lines 20-30, the present sequences define a number of coding single nucleotide polymorphisms - specifically: a C/T polymorphism at nucleotide position 28 of SEQ ID NO:3, a silent polymorphism that results in a leucine at amino acid position 10 of SEQ ID NO:4; and a G/A polymorphism at nucleotide position 379 of SEQ ID NO:3, which can result in an alanine or threonine at amino acid position 127 of SEQ ID NO:4. As such polymorphisms, and particularly combinations of polymorphisms, are the basis for forensic analysis, which is undoubtedly a "real world" utility, the present sequences must in themselves be useful. It is important to note that the presence of more useful polymorphic markers for forensic analysis would not mean that the present sequences lack utility.

As an additional example of the utility of the present nucleotide sequences, the specification details on page 5, lines 9-12, that the present nucleotide sequences have utility in assessing gene expression patterns using high-throughput DNA chips. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. As the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof

in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, *Science* 291:1304). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, *Science* 291:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Additionally, Applicants would like to invite the Examiner's attention to the fact that a sequence sharing 100% percent identity at the protein level over an extended region of the claimed sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists at the National Center for Biotechnology Information who are *wholly unaffiliated with Applicants* as a "serine protease" (GenBank accession number XM_171629; GenBank report shown in **Exhibit C**, alignment shown in **Exhibit D**). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given this GenBank annotation, there can be no question that those skilled in the art would clearly believe that Applicants' sequence is a protease.

Applicants' Affidavit of Belief in the Utility of the Invention

(CCPA 1964, *in re* *Maniowski*, 489 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide,

as described in the specification at least at page 10, line 18, the present nucleotide sequence has a specific utility in determining the genomic structure of the protein encoding regions of the corresponding human chromosome. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence.

Only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). This is demonstrated by the fact that the bioinformatically predicted sequence described above (GenBank accession number XM_171629; **Exhibit C**), appears to contain a large region of intronic sequence (an additional 157 amino acids are included in the predicted sequence between amino acids 214 and 215 of SEQ ID NO:4) that has been misidentified as coding sequence. Additionally, the first 69 amino acids, including an alternative splice site, is missing from the bioinformatically predicted amino acid sequence. These mistakes are clearly shown in **Exhibit E**, which is an alignment of SEQ ID NO:4 and XM_171629, based on the nucleotide sequence shown in XM_171629. The initiator methionine residue identified in the predicted amino acid sequence shown in XM_171629 (see **Exhibit C**) is indicated by the red arrow, 69 amino acids downstream from the

scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in

support of the Applicants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra* at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Rather, as set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

The Action states that the present sequence lacks utility because the "relationship [of the claimed sequence] to any disease" is not provided (Action at page 3). However, this is not the standard required for utility under 35 U.S.C. § 101. In *In re Brana*, (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under

35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. The Action goes on to state that the claimed sequences lack utility because "further research" (Action at page 3) would be required in certain aspects of the invention. Even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra; Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Furthermore, the Examiner seems to be requiring the specification to "show any enzyme assays that demonstrate that the protein consisting of SEQ ID NO:4 has any protease activity" (the

Examiner has applied this mandatory legal precedent, as it has not been established that there is a statutory requirement for the disclosure of a specific example". *In re Gav*, 309 F.2d 769, 135 USPQ

311 (CCPA, 1962).

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. The PTO has issued numerous patents on polynucleotide sequences that have not been directly shown to be associated with "any disease", the condition apparently set forth by the Examiner as allegedly necessary to comply with 35 U.S.C. § 101. The Examiner is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotide fragments), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples). None of these issued U.S. Patents contain examples of the "real-world" utilities that the Examiner seems to be requiring in the present Action. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section IV below), Applicants submit that the presently claimed polynucleotide must also meet the requirements of 35 U.S.C. § 101. Holding Applicants to a different standard of utility would be arbitrary and capricious, and cannot stand.

For each of the foregoing reasons, Applicants submit that as the presently claimed nucleic acid molecules have been shown to have a substantial, specific, credible and well-established utility, the rejection of claims 1 and 2 under 35 U.S.C. § 101 has been overcome, and request that the rejection be withdrawn.

IV. Rejection of Claims 1 and 2 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1 and 2 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by a specific, substantial, and credible utility or a well-established utility. Applicants respectfully traverse.

Applicants submit that as claims 1 and 2 have been shown to have "a specific, substantial, and credible utility," the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, is not proper.

Applicants therefore request that the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. **Rejection of Claims 1 and 2 Under 35 U.S.C. § 112, First Paragraph**

The Action next rejects claims 1 and 2 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

The Action states that claims 1 and 2 lack sufficient written description because "there is no disclosure of any particular structure to function/activity relationship" between the claimed fragments of SEQ ID NO:3 and the full length sequence of SEQ ID NO:3 (the Action at page 4). This argument fails to support the alleged lack of written description for at least two reasons. First, there is a "particular structure to function/activity relationship" disclosed between the claimed fragments of SEQ ID NO:3 and the full length sequence of SEQ ID NO:3 - specifically, that these fragments of SEQ ID NO:3 are **novel**, and therefore **unique**, identifiers of SEQ ID NO:3. The specification, at least at page 5, lines 5-12, details that these fragments can thus be used in a number of different methods, including, but not limited to, in conjunction with PCR to screen libraries, isolate clones, and prepare cloning and sequencing templates, as well as in assessing gene expression patterns using microarray or gene chip formats. Second, and perhaps most importantly, there is **no** requirement whatsoever that novel fragments of a novel sequence have the exact same function as the full length sequence in order to be patented. If this were to be the case, hundreds, if not thousands, of issued U.S. Patents would be instantly invalidated, as they each claim nucleotide fragments that have not been demonstrated to have the exact same function as the full length nucleotide sequence. Applicants therefore submit that the claimed sequence meets the written description requirement of 35 U.S.C. § 112, first paragraph.

As set forth in Applicants response filed on February 7, 2002, to the Office Action mailed on October 26, 2001, 35 U.S.C. § 112, first paragraph, requires that the specification contain a

enablement of the invention.

"One skilled in the art that, as of the filing date sought, he or she was in possession of the invention."

Vas Cath, at 1117, emphasis in original. However, it is important to note that the above finding uses

the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other

material, by using the generic formula, is sufficient.

If claims to genetic material - a genetic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written

description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself*.

Using the nucleic acid and amino acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising at least 60 contiguous nucleotides from the nucleotide sequence of SEQ ID NO:3, or a nucleotide sequence that encodes SEQ ID NO:4, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Claims 1 and 2 thus meet the written description requirement.

For each of the foregoing reasons, Applicants submit that the rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, has been overcome, and request that the rejection be withdrawn.

VI. Rejection of Claim 2 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the invention.

The Action next rejects claim 2 as allegedly indefinite based on the term "highly stringent hybridization conditions", because the specific "hybridization and washing conditions are not recited in the claim" (Action bridging pages 4 and 5). Applicants stress that "a claim need not 'describe' the

term is sufficiently definite, as a number of stringent hybridization conditions are defined in the

specification and would be known to those of skill in the art, solely in order to progress the case more rapidly toward allowance the claim has been revised to recite specific highly stringent hybridization conditions. As the specification provides specific teaching regarding these highly stringent hybridization conditions, at least at page 4, lines 1-9, Applicants submit that revised claim 2 even more clearly meets the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request withdrawal of this rejection.

VII. Rejection of Claim 1 Under 35 U.S.C. § 102(b)

The Action next rejects claim 1 under 35 U.S.C. § 102(b), as allegedly anticipated by Strausberg *et al.* (Accession #AA884376; "Strausberg"). While Applicants do not necessarily agree with the present rejection, as claim 1 has been amended to comprise at least 60 contiguous nucleotides from SEQ ID NO:3, which the Examiner agrees is not taught by Strausberg (Action at page 5), Applicants submit that the rejection of claim 1 under 35 U.S.C. § 102(b) has been overcome, and respectfully request withdrawal of the rejection.

Applicants note for the record that the art cited by the Examiner in the Action (AA884376) was available to the Examiner (publication date January 4, 1999) at the time of the previous Office Action in this case, which was mailed on October 26, 2001 ("the previous Action"). Furthermore, Applicants note that AA884376 is better art than the art cited in the previous Action (Tsuruoka *et al.*, Accession #E13202, Alignment No. 1). Applicants respectfully remind the Examiner that, as set forth in the Manual of Patent Examination Procedure, Section 706.02, "(p)rior art rejections should ordinarily be confined strictly to the best available art" (emphasis added). This allows the examination process to proceed in as timely a fashion as possible, which is even more important since the advent of the regulations setting patent term to run 20 years from the filing date of the application. Applicants trust that AA884376 is the best available art, and as this art has been overcome in the present response, that no more rejections based on prior art that is presently available to the Examiner will be made.

VIII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Fronda have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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